Interferon alfa-2a maintenance after salvage autologous stem cell transplantation in atypical mycosis fungoides with central nervous system involvement

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Abstract

Mycosis fungoides is a primary cutaneous T-cell lymphoma with unfavorable prognosis for the advanced stages of the disease. Refractory disease and advanced-stage disease require systemic therapy.

We report on a rare case of an atypical predominantly CD8+ folliculotropic mycosis fungoides (MF), a subtype of MF with poorer prognosis, in a 59-year-old woman, initially diagnosed with MF restricted to the skin- of T3N0M0B0/stage IIB according to the current WHO/EORTC classification. First-line treatment with local percutaneous radiotherapy in combination with systemic interferon alfa-2a resulted in complete remission. However, 21 months later the disease progressed to T3N0M1B0/stage IVB with development of cerebral manifestation and thus very poor prognosis. Allogeneic stem cell transplantation (SCT) was not a therapeutic option due to the lack of a suitable donor. We initiated methotrexate and cytarabin chemotherapy, followed by high-dose chemotherapy with thiotepa and BCNU with autologous SCT. Despite rapid response and complete remission of the cerebral lesions, disease recurrence of the skin occurred soon after. Interestingly, re-administration of interferon alfa-2a as a maintenance treatment after the salvage autologous SCT resulted in a durable complete remission during the follow-up period of currently 13 months after autologous SCT.

Introduction

Cutaneous T-cell lymphomas represent a group of extranodal non-Hodgkin lymphomas originating from malignant clonal transformation of skin homing and/or skin resident-T cells[1]. Mycosis fungoides (MF) encompasses approximately 60% of all cutaneous T-cell lymphomas and is therefore the most frequent type[2]. Median age of first presentation is 57 years with a male/female ratio of 2:1[3]. Approximately, 0.36-0.9 per 100,000 persons per year are diagnosed with MF[4,5]. MF can have an indolent course with a 5-year survival rate of nearly 100% in stage IA to less than 10% in stage IVB disease[6]. MF exhibits a broad and increasing spectrum of clinical, histological, and immunophenotypic variants, but on average, 10% of all stage IA MF- patients with skin- limited patches or plaques will progress to more advanced disease[7]. On the contrary, folliculotropic MF is associated with impaired prognosis with 5- and 15-year survival rates of approximately 60-80% and 41%, respectively[8-12]. Most often, extracutaneous involvement occurs in the liver, spleen and lungs[13,14], but the occurrence of cerebral involvement in MF is known to be very rare, and intraparenchymal disease is even less frequent than meningeal disease[15].

We report on a patient with atypical MF with central nervous system involvement, in whom salvage high-dose chemotherapy with autologous SCT and interferon alfa-2a maintenance therapy resulted in durable complete remission.

Case report

A 59-year-old woman was referred to our hospital with newly diagnosed MF. Five months before, she first noticed a skin lesion rapidly growing on the right side of her chin and transiently enlarged right submandibular lymph nodes without systemic symptoms (Figure 1A). The patient's medical history was unremarkable, with the exception of an uneventful complete excision of a basal cell carcinoma on the nose several months before. Skin biopsy of the above described lesion revealed folliculotropic small-sized predominantely CD8+ T-cell lymphoma compatible with MF, plaque stage. Histology showed proliferation of atypical lymphocytes located to hair follicules without either mucin deposition nor interfollicular epidermotropism. Immunohistochemistry demonstrated expression of CD3, CD5 and predominantly CD8 rather than CD4 expression on hair follicules infiltrating atypical lymphocytes (Figure 1B). Moreover, complete dermatological examination revealed multiple, disseminated, hitherto disregarded by the patient patches, plaques and agminated papules (Figure 1C). Lymph node sonography and whole-body combined positron-emission tomography and computed tomography (PET-CT) showed no extracutaneous involvement. The patient was thus initially diagnosed with a skin-limited MF of folliculotropic subtype (one nodular facial lesion and

multiple disseminated skin patches on the anterior and posterior trunk), and classified as a T3N0M0B0/stage IIB according to the current WHO/EORTC classification.

External-beam radiotherapy with a fractionated total dose of up to 32Gy was used as a first-line treatment of the facial nodule and systemic interferon alfa-2a 3x3Mio per week and PUVA therapy for the disseminated patches was applied. This treatment resulted in a full remission of the MF 16 months after disease onset. However, 5 months later new subtle depressive symptoms, including mild fatigue and a tendency for a decreased willingness to engage in conversation and make decisions occurred. At first, we interpreted those symptoms as a side effect of interferon alfa-2a and stopped the treatment. Nevertheless, within a few weeks, the patient developed pronounced personality changes and had difficulties finding words.

Magnetic resonance imaging (MRI) of the brain showed T2 hyperintense large lesion in the left frontal lobe with involvement of the corpus callosum and basal ganglia (Figure 2A). Neuropathological examination of stereotactic brain biopsy of the frontal lobe demonstrated diffuse infiltration of the CNS tissue by a small round blue cell neoplasm with increased mitotic activity as well as increased apoptosis. The findings were compatible with brain metastasis of mycosis fungoides. The neoplastic cells were immunoreactive for CD3, CD7, TCR-β F1 (fig. 2B) and TIA1 (not shown). Scattered neoplastic cells showed CD2 and CD5 immunoreactivity, indicating antigen loss (see figure 2B). Only few cells showed weak CD8 positivity (not shown), CD30 remained negative (fig 2B). Staining for CD4 and CD56 showed extremely high background immunoreactivity in the CNS tissue and were classified as «inconclusive» (not shown). Proliferation index (Mib-1) was >95% (fig. 2B). Neoplastic cells were negative for CD20, TdT, CD79a, TCL-1, Perforin, TCR-gamma, ALK1 as well as for Epstein–Barr encoding region (EBER) in situ hybridization (not shown).

MF progression to T3N0M1B0/stage IVB is associated with a very bad prognosis. Since no matching stem cell donor for allogeneic SCT was available, we initiated methotrexate and cytarabin chemotherapy, followed by high-dose chemotherapy with thiotepa and BCNU with autologous SCT.

Despite rapid response and complete remission of the cerebral lesions (Figure 2C), histologically confirmed disease recurrence of the skin occurred 10 months after the autologous SCT (Figure 2D and E). Quantitative assessment of the total skin disease burden post-autoSCT with the modified severity weighted assessment tool (mSWAT) scored 15 out of 400 points (Figure 3A).

Interestingly, re-administration of interferon alfa-2a 3x3Mio per week as a maintenance treatment after the salvage autologous SCT resulted in a durable complete remission (mSWAT 0) during the follow-up period of currently 17 months after autologous SCT (Figure 3B). All biopsied patient's skin and brain lesions displayed an identical unequivocally monoclonal T-cell population (Figure 3C).

Discussion

This is rare manifestation of an atypical, predominantly CD8+ primary cutaneous T cell lymphoma with subsequent cerebral involvement. According to the current WHO/EORTC classification, mycosis fungoides (MF) and primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (pcAETCL) represent the two major differential diagnosis[16]. pcAETCL may often spread to the central nervous system and has an estimated 5-year survival of 0%[17]. To establish the diagnosis of pcAETCL, sets of diagnostic criteria, based on combination of clinical, histopathological, and immunohistochemical features have been suggested[18]. However, no specific criterion pathognomonic for pcAETCL exists, its clinical features can be indistinguishable from advanced MF, and exclusion of MF is crucial before establishing the diagnosis of pcAETCL[19-21]. In this particular case, the clinical appearance with one non-ulcerative nodular facial lesion and multiple disseminated skin patches and plaques on the anterior and posterior trunk was typical for MF and did not favor pcAETCL[20]. Furthermore, diagnostic criteria for MF were formally fulfilled and the clinical course of the disease, including the clinical manifestation of the relapse lesions post auto-SCT strongly favored the diagnosis of MF [22-24]. In MF patients, cerebral involvement is rare and presents most frequently as cranial nerve dysfunction or fluctuation of higher cognitive functions[25]. In line with this, loss of eagerness to engage in conversations dominated the clinical appearance of the patient presented here. The risk of cerebral involvement in MF patients increases with large-cell transformation (LCT)[16]. Interestingly, LCT could not be detected in the present case. However, in contrast to our patient who did not show any extracutaneous organ involvement other than the brain, most MF patients with cerebral disease without LCT develop significant skin lesions or visceral involvement before disease spread to the central nervous system (CNS)[25]. The incidence of CNS involvement in MF clinical studies is less than 1.3-1.6%[13,26], whereas autopsy series found post mortem CNS involvement in 10-15% of MF patients[25,27,28]. Stein et al. found MF patients with two or more of the T3-4, N3, M1 and B1 classification factors to have a one in six chance for cerebral involvement and defined a median survival with treatment of 3 months after onset of neurologic symptoms[13]. Patients who refused treatment died on average within one month[13]. Recently Yang et al reported a systemic review on 77 MF patients with CNS metastasis, 10 of whom achieved complete remission. In this analysis, the median time between the diagnosis of MF and the detection of cerebral metastasis was 36 months. None of those patients received autologous SCT, most common treatments being radiation, intrathecal methotrexate and single agent chemotherapy, none of them associated with a different clinical outcome[29].

As a sensitive and specific detector of cerebral metastasis MRI, CT scan and cerebrospinal fluid analysis were tested, but none of these was found to be completely reliable.[29] Some researchers have suggested that elevated β2-microglobulin and lactate dehydrogenase levels (LDH) may be markers of CNS involvement[13,27,30]. However, while elevated serum LDH is a known marker of poor prognosis in MF[31], it is still unclear if LDH and serum β2-microglobulin could be useful as routine parameters in the diagnostic and follow-up of MF with respect to cerebral manifestations. Whereas prophylactic therapy such as brain radiation is applied to patients with non-Hodgkin lymphoma[32,33], it is not common in patients with MF[34]. As Stein et al. suggest, patients at high-risk of CNS involvement could benefit from whole brain and proximal cranial nerve radiation therapy at little expense and toxity[13].

The management of advanced MF is currently based on mono- or combinational therapy, including interferon-α, retinoids (bexarotene), photopheresis, chemotherapy, radiotherapy, as well as targeted therapies such as the monoclonal antibody brentuximab[35-37]. Most treatment options only induce remissions of limited duration[29-31]. An additional challenge in the management of advanced MF patients is their severely compromised immunity, with an aberrant TH2- phenotype as well as abnormal natural killer cell-, cytotoxic T-cell- and dendritic-cell function[9,38,39].

SCT is a curative treatment option for advanced MF, with overall survival or relapse- free survival significantly longer in patients with allogenic than with autologous SCT[40]. MF patients receiving allogeneic SCT further benefit from the graft versus leukemia effect, mediated by allogeneic donor T-cells that target and eliminate tumor cells.

The very poor/unfavorable prognosis of the cerebral involvement in the case of the patient presented here, necessitated an immediate treatment, but a suitable donor for allogeneic SCT could not be identified in due time. As a consequence, we opted for high dose chemotherapy with autologous SCT. In cutaneous T-cell lymphoma, especially MF, this approach usually induces a temporary remission, but relapses follow early, from 61 days to 15 months post transplantation[40-44]. Moreover, the short time to relapse is associated with a shorter survival time[30].

In line with this data, our patient's MF relapsed early after the autologous SCT, but in a less aggressive form, with skin limited patch form of the disease only. Following re-administration of interferon alfa-2a 3x3Mio per week as maintenance therapy after the salvage autologous SCT, a durable complete remission for a follow-up period of currently 17 months after SCT was achieved.

Clinical research assessing the efficacy of alfa-type IFNs in the management of CTCL have considered two forms of recombinant IFN alfa, IFN alfa-2a (Roferon®) and IFN alfa-2b (Intron-A®) and its pegilated versions Pegasys® and PegIntron®, respectively[45]. IFN alfa-2a and IFN alfa-2b share nearly

identical structures, seem to bind to the same type I IFN receptor and to have similar efficacy in the treatment of CTCL. However, while Roferon® is no longer manufactured in the United States, it is currently the only IFN alfa officially licensed for the treatment of CTCL in Europe, hence our decision to use interferon alpha-2a versus 2b in this particular case[45,46].

Reported data on long-term favorable post-autologous SCT outcome in advanced MF is scarce. Less aggressive disease has been reported after autologous SCT[42]. Di et al. reported a 25-year-old patient with multiple skin lesions, lymphadenopathy and neurological symptoms, who received autologous STC after progression on chemotherapy. Fourteen years after, this patient was still in complete remission[47]. Our patient has now an ongoing 17-month remission. In summary, we report on an unusual case of MF with cerebral involvement, in which a durable complete remission was achieved upon autologous SCT and interferon alfa-2a maintenance therapy.

Figure Legends:

Figure 1: A) Clinical appearance of the skin nodule in the right mandibular region. B) Folliculotropic MF with infiltration of a hair follicle by small- to medium-sized lymphocytes without mucin deposition and some nuclear atypia (yellow arrowheads) (H&E, upper part of the image). Lymphocytes showed CD3 and predominantly CD8 positivity in the fraction of the folliculotropic lymphocytes (IHC, lower part of the image). C) Initial clinical manifestation of mycosis fungoides MF with multiple, disseminated erythematous patches, plaques and papules.

Figure 2: A) Magnetic resonance imaging (MRI) before autologous SCT of the brain with T2 hyperintense large lesion in the left frontal lobe with involvement of the corpus callosum and basal ganglia. B) Stereotactic brain biopsy of the frontal lobe: H&E staining demonstrates diffuse infiltration of the CNS tissue by a small round blue cell neoplasm with increased mitotic activity (yellow arrowheads) and increased apoptosis. Immunoreactivity of the neoplastic cells for CD3, CD7, TCR-beta F1 and TIA1 (not shown). Partial antigen loss for CD2 and CD5; no immunoreactivity for CD30. Proliferation index (MIB-1) >95%. C) MRI after autologous SCT of the brain shows complete remission of the brain metastasis in the left frontal lobe. D) Clinical appearance of recurrent lesion after auto-SCT; erythematous patch on the left upper arm. E) Skin biopsy of the recurrent lesion depicted in (D) with band-like infiltrate of lymphocytes within the superficial dermis and marked epidermotropism of atypical lymphocytes (yellow arrowheads). Lymphocytes showed predominantly CD8 positivity especially in the fraction of the epidermotropic lymphocytes (IHC, middle part of the image). ***Abbrev.:*** **CD**: cluster of differentiation; **TdT**: Terminal deoxynucleotidyl transferase ; **TCL-1**: T-

cell leukemia/lymphoma protein 1 ; **TCR-beta F1**: T cell receptor beta locus; **TIA1**: TIA1 cytotoxic granule associated RNA binding protein

Figure 3: A) MF relapse after autologous SCT. Clinical appearance of the skin lesions. B) Durable complete remission upon interferon alfa-2a maintenance therapy. C) Correlation of T cell receptor (TCR)-γ clonality in multiple skin and brain lesions. All patient's skin and brain lesions (skin biopsy No. 1 & 2 before autoSCT, brain biopsy No. 1 & 2 before autoSCT and skin biopsy of recurrent lesion after autoSCT) display an identical clear clonal T-cell population (167 base pairs; bp/Vγ9 + Jγ 1.3/2.3), no clonally rearranged T cells were found in patient's blood. Results from EuroClonality (BIOMED-2) TCR assay, with primers targeting all Vγ1-11 genes and all Jγ exons. All assays were performed in duplicates with lower (HEX/B) and higher (HEX/B+) DNA concentration.

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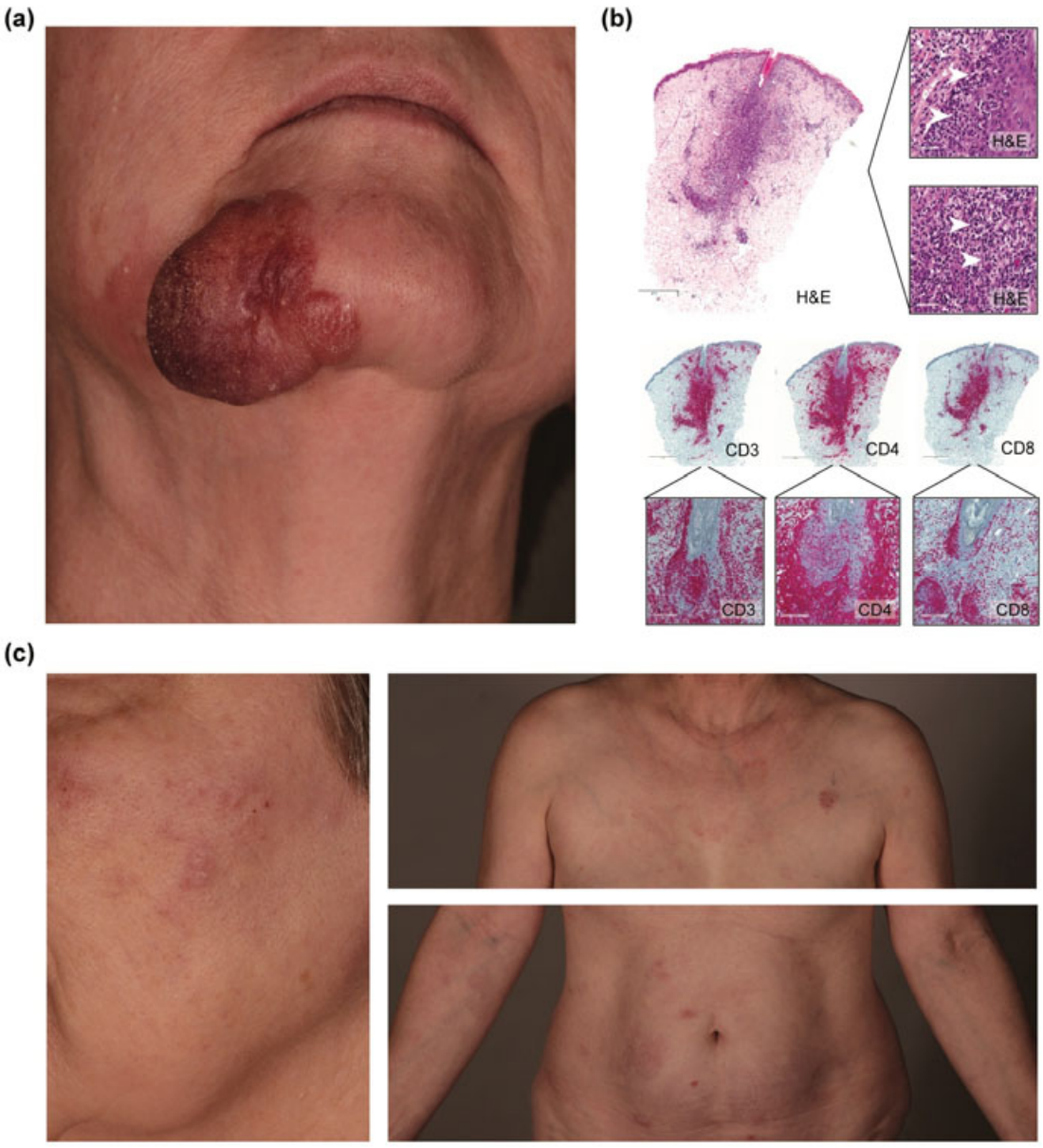

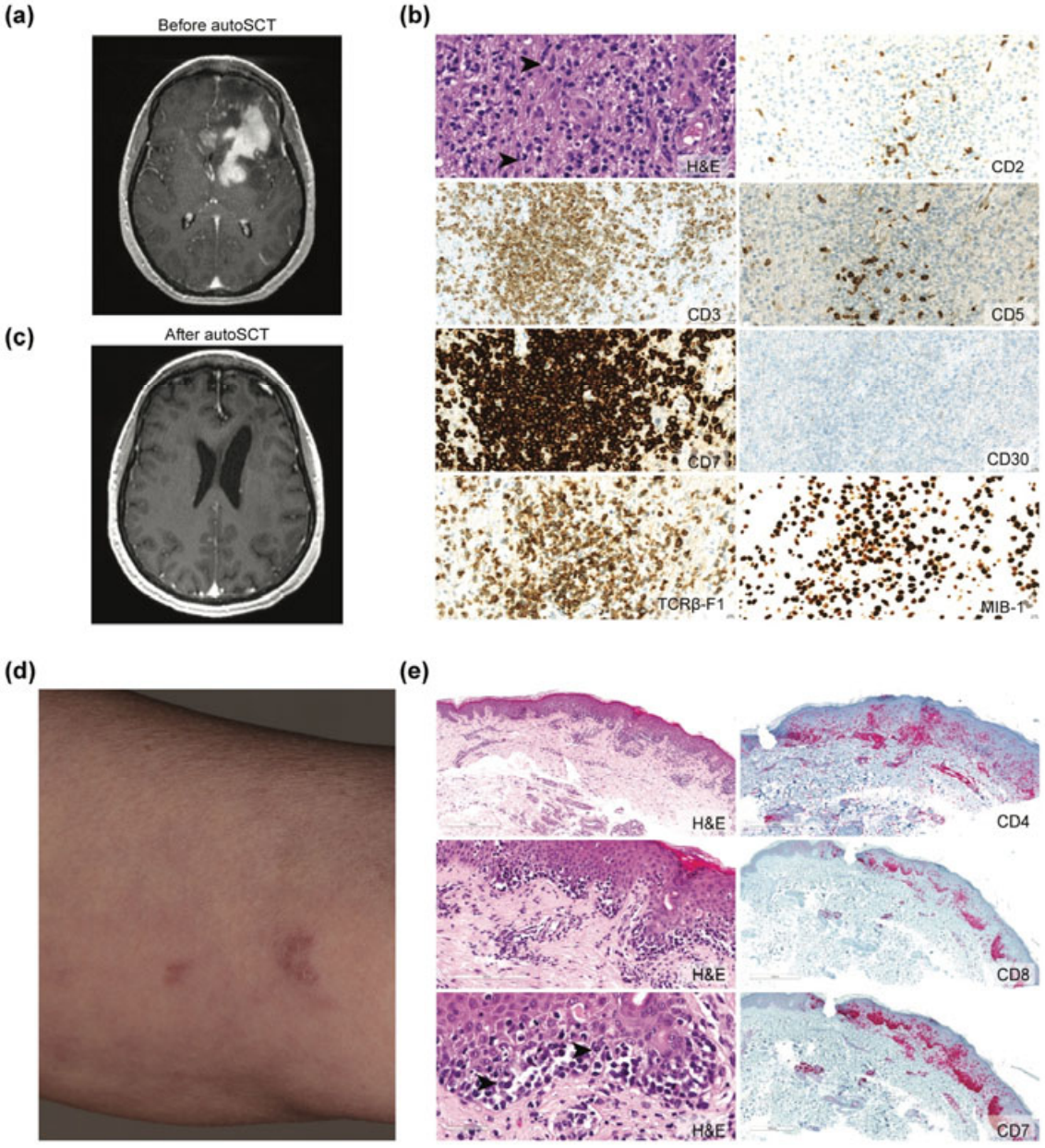

(a)

Reccurence after autoSCT

(b)

On IFN maintenance

(c)